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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/552,178 | 07/02/2007 | Masaaki Oka | 3462.1015-000 | 6214 |

21005 7590 03/10/2010

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| EXAMINER | |
|---|---|
| AEDER, SEAN E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 03/10/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,178 | OKA ET AL. | |
| | Examiner | Art Unit | |
| | SEAN E. AEDER | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5 and 7-15* is/are pending in the application.

4a) Of the above claim(s) *13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## *Detailed Action*

The Amendments and Remarks filed 2/2/10 in response to the Office Action of 11/2/09 are acknowledged and have been entered.

Claims 1-5 and 7-15 are pending.

Claims 13-15 have been withdrawn.

Claims 1-5 and 7-12 have been amended by Applicant.

Claims 1-5 and 7-12 are currently under examination.

This Office Action contains new rejections necessitated by amendments.

## *Rejections Withdrawn*

All previous rejections are withdrawn.

## *New Rejections Necessitated by Amendments*

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Applicant is invited to review the OG notice of 11/22/05 (http://www.uspto.gov/web/offices/com/sol/og/2005/week47/patgupa.htm). When a method claim does not result in a physical transformation of matter, the claim may be statutory when it recites a **concrete**, **tangible**, and useful result. In the instant case, the

claims are directed to methods of defining the differentiation grade of a tumor based on expression levels or patterns of genes. The claims lack any recited method of physical transformation of matter. Further, although the recited method may be useful, the method does not recite a concrete or tangible result. It appears that the result is an expression level(s); however, the expression level(s) is not concrete because the claims do not distinctly point-out *exactly* what each expression level(s) *means*. Further, the result is not tangible because the claims do not recite a means of communicating the result to a user. This rejection could be obviated by incorporating a method of physical transformation, such as an active method of performing an assay, in independent claim(s) 1 and 10-12. Alternatively, this rejection could be obviated by amending independent claim(s) 1 and 10-12 to recite a method with a concrete, tangible, and useful result. Note that this is not a utility rejection.

In the Reply of 2/2/10, Applicant argues that the pending claims require a physical transformation of matter because independent claim 1 has been amended to add a step of performing an assay for determining expression levels or patterns of genes and/or proteins.

The amendments to the claims and the arguments found in the Reply of 2/2/10 have been carefully considered, but are not deemed persuasive. In regards to the argument that the pending claims require a physical transformation of matter because independent claim 1 has been amended to add a step of performing an assay for determining expression levels or patterns of genes and/or proteins, claims 1 does not require one to perform a step requiring a physical transformation of matter or require

one to perform an assay for determining expression levels or patterns of genes and/or proteins. Rather, independent claim 1 has been amended to passively state: "...and wherein the expression levels or patterns of genes and/or proteins are determined by performing an assay for the gene and/or protein levels and patterns". Such a passive statement does not require one to perform any kind of assay; rather, such a statement may merely informs one of the well-known facts that expression levels or patterns of genes and/or proteins are determined by performing an assay for the gene and/or protein levels and patterns. It is noted that this rejection would be obviated if independent claim 1 is amended to recite an active method comprising "determining the expression levels or patterns of genes and/or proteins by performing an assay for the gene and/or protein levels and patterns".

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02).

Okabe et al teaches a method of defining the differentiation grade of a tumor with genes selected by statistical analysis comprising determining the number of genes to

define the differentiation grade of tumor and using microarrays based on expression level or pattern of genes of human liver tumor tissues, wherein the differentiation grade of tumor is selected from the group consisting of non-cancerous liver, pre-cancerous liver, well differentiated HCC, moderately differentiated HCC, and poorly differentiated HCC and wherein the genes are differentially expressed between non-cancerous liver and pre-cancerous liver, precancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC (see pages 2136-2137, in particular). Okabe et al further teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular).

Okabe et al does not specifically teach methods wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC. However, these deficiencies are made up in the teachings of Adorjan et al.

Adorjan et al teaches method of selecting cancer markers by using a Fisher ratio, referred to by Adorjan et al as a "Fisher criterion" (see paragraphs 0104-0105, in particular). Adorjan et al further teaches a Fisher ratio is a classical measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking

for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to the determine the differentiation grade of a tumor with genes identified by Okabe et al by performing Fisher ratios with the expression data of Okabe et al wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC in order to accurately identify particular tumor types because Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular) and Adorjan et al teaches a Fisher ratio is a "classical" measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for determine the differentiation grade of a tumor with genes identified by Okabe et al by performing Fisher ratios with the expression data of Okabe et al wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous

liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC in order to accurately determine which markers of Okabe et al are associated with particular tumor types because Adorjan et al teaches how to perform a Fisher ratio and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 2/2/10, Applicant argues that the combined references do not disclose methods of classifying HCC into five groups. Applicant further argues that the cited references do not teach or suggest that the Fisher criterion can be employed to determine differences in gene expression profiles in five different grades of cancer. Applicant states that the usage of the Mann-Whitney test in the teachings of Okabe appears proper and complete and there is no motivation to look to the teachings of Adorjan to substitute the Mann-Whitney test of Okabe with the Fisher criterion of Adorjan. Applicant further argues that one would not have been able to arrive at the claimed invention with a reasonable expectation of success absent (1) specific knowledge that HCC progression can be classified into five distinct groups and (2) empirical genome-wide expression data for each of the five groups. Applicant further argues unexpected results by stating genes not identified by Okabe were identified by the present invention as differentially regulated between G1 and G2/G3 and that the

present invention provides expression profiles that are superior to the prior art available at the time the invention was made. Applicant further states that the present invention provides a method for better predicting the grade of an unknown tumor sample by classifying HCC progression into five distinct groups.

The amendments to the claims and the arguments found in the Reply of 2/2/10 have been carefully considered, but are not deemed persuasive. In regards to the argument that the combined references do not disclose methods of classifying HCC into five groups, Applicant is arguing limitations not recited in the claims. The claims do not require one to classify HCC into five groups. It is noted dependent claim 4 and independent claims 10-12 recite methods involving using genes that are differentially expressed between non-cancerous liver and pre-cancerous liver, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC. The combined methods do use genes that are differentially expressed between well differentiated HCC and moderately differentiated HCC (see pages Figure 3 and pages 2136-2137 of Okabe et al, in particular). Such methods that use genes that are differentially expressed between well differentiated HCC and moderately differentiated HCC are methods that use genes that are differentially expressed between non-cancerous liver and pre-cancerous liver, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC as required by dependent claim 4 and independent claims 10-12.

In regards to the argument that the cited references do not teach or suggest that the Fisher criterion can be employed to determine differences in gene expression

profiles in five different grades of cancer, Applicant is arguing limitations not recited in the claims. The claims do not require one to determine differences in gene expression profiles in five different grades of cancer. Rather, the claims only require one to determine expression of genes that are differentially expressed in as few as two different grades of cancer.

In regards to the argument that the usage of the Mann-Whitney test in the teachings of Okabe appears proper and complete and there is no motivation to look to the teachings of Adorjan to substitute the Mann-Whitney test of Okabe with the Fisher criterion of Adorjan, one of ordinary skill in the art at the time the invention was made would have been motivated to the determine the differentiation grade of a tumor with genes identified by Okabe et al by performing Fisher ratios with the expression data of Okabe et al wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC in order to accurately identify particular tumor types because Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular) and Adorjan et al teaches a Fisher ratio is a “classical” measure to assess the degree of separation between two classes and the Fisher ratio

gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular).

In regards to the argument that one would not have been able to arrive at the claimed invention with a reasonable expectation of success absent (1) specific knowledge that HCC progression can be classified into five distinct groups and (2) empirical genome-wide expression data for each of the five groups, Applicant is arguing limitations not recited in the claims. The claims do not require one to classify HCC progression into five groups. Further, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for determine the differentiation grade of a tumor with genes identified by Okabe et al by performing Fisher ratios with the expression data of Okabe et al wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC in order to accurately determine which markers of Okabe et al are associated with particular tumor types because Adorjan et al teaches how to perform a Fisher ratio and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In regards to the argument that genes not identified by Okabe were identified by the present invention as differentially regulated between G1 and G2/G3, Applicant is arguing limitations not recited in the claims. Genes disclosed as differentially regulated between G1 and G2/G3 are not read into the instant claims.

In regards to the argument that that the present invention provides expression profiles that are superior to the prior art available at the time the invention was made, Applicant is arguing limitations not recited in the claims. Genes of disclosed expression profiles are not read into the instant claims.

In regards to the argument that the present invention provides a method for better predicting the grade of an unknown tumor sample by classifying HCC progression into five distinct groups, Applicant is arguing limitations not recited in the claims. The claims do not require one to classify HCC progression into five distinct groups.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) as applied to claims 1-11 above, and further in view of Bloch et al (US 6,728,642 B2; 4/27/04).

The combined teaching of Okabe et al and Adorjan et al is discussed above.

The combined teaching of Okabe et al and Adorjan et al does not specifically teach a method wherein a minimum distance classifier with data of selected genes is designed and wherein a self-organizing map is generated with data of genes. However, these deficiencies are made up in the teachings of Boch et al.

Boch et al teaches a "minimum distance classifier" is a well-known cluster identification algorithm (see paragraph 0098, in particular). Boch et al further teaches illustrating classified genes into self-organizing maps (see Figures 10-11, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to design minimum distance classifiers with the genes identified by the Okabe et al and Adorjan et al and generate a self-organizing map with data of the genes identified by the method of Okabe et al and Adorjan et al because Boch et al teaches a "minimum distance classifier" is a "well-known" cluster identification algorithm (see paragraph 0098, in particular), Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular), and Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for designing minimum distance classifiers with the genes identified by the Okabe et al and Adorjan et al and generate a self-organizing map with data of the genes identified by the method of Okabe et al and Adorjan et al because Boch et al teaches a "minimum distance classifier" is a "well-known" cluster identification algorithm (see paragraph 0098, in particular) and Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular). Therefore, the invention as a whole

would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 2/2/10, Applicant repeats arguments that have been addressed above.

### *Summary*

No claim is allowed.

### *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642